ANTIBODY CONJUGATES COMPRISING TOLL-LIKE RECEPTOR AGONIST

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 62/247,896, filed 29 Oct. 2015, which is incorporated by reference herein in its entirety.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on Oct. 5, 2016, is named PAT057064-US-NP_SL.txt and is 54,974 bytes in size.

FIELD OF THE INVENTION

[0003] The invention provides antibody conjugates comprising toll-like receptor agonists and the use of such conjugates for the treatment of cancer.

BACKGROUND OF THE INVENTION

[0004] Innate immunity is a rapid nonspecific immune response that fights against environmental insults including, but not limited to, pathogens such as bacteria or viruses. Adaptive immunity is a slower but more specific immune response, which confers long-lasting or protective immunity to the host and involves differentiation and activation of naive T lymphocytes into CD4+T helper cells and/or CD8+ cytotoxic T cells, to promote cellular and humoral immunity. Antigen presentation cells of the innate immune system, such as dendritic cells or macrophages, serve as a critical link between the innate and adaptive immune systems by phagocytosing and processing the foreign antigens and presenting them on the cell surface to the T cells, thereby activating T cell response.

[0005] Toll-like receptors (TLRs) are pattern recognition receptors (PRR) that are expressed predominantly on dendritic cells, macrophages, monocytes, natural killer cells, and T lymphocytes. TLRs bind to pathogen-associated molecular patterns (PAMPS) from bacteria, fungi, protozoa and viruses, and act as a first line of defense against invading pathogens. TLR activation leads to increased antigen uptake, maturation, and T-cell stimulatory capacity of the dendritic cells. TLRs comprise an extracellular N-terminal leucine-rich repeat (LRR) domain, followed by a cysteine-rich region, a transmembrane domain, and an intracellular (cytoplasmic) tail that contains a conserved region named the Toll/IL-1 receptor (TIR) domain. The LRR domain is important for ligand binding and associated signaling and is a common feature of PRRs. The TIR domain is important in protein-protein interactions and is associated with innate immunity. TLRs are essential to induce expression of genes involved in inflammatory responses, and play critical roles in the development of antigen-specific acquired immunity.

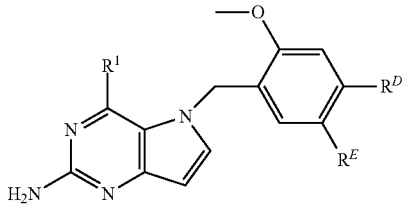
[0006] There remains a need for new immunotherapies for the treatment of diseases, in particular cancer.

SUMMARY OF THE INVENTION

[0007] The invention provides antibody conjugates comprising toll-like receptor agonists, pharmaceutically acceptable salts thereof, pharmaceutical compositions thereof and combinations thereof, which are useful for the treatment of diseases, in particular, cancer. The invention further provides methods of treating, preventing, or ameliorating cancer comprising administering to a subject in need thereof an effective amount of an antibody conjugate of the invention. The invention also provides compounds comprising TLR7 agonists and a linker which are useful to conjugate to an anti-HER2 antibody and thereby make the immunostimmulatory conjugates of the invention. Various embodiments of the invention are described herein.

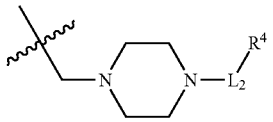
[0008] In one aspect of the invention are compounds having the structure of Formula (I), and the pharmaceutically acceptable salts thereof, which are TLR7 agonists:

Formula (I)

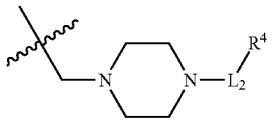


wherein:

[0009] R^D is



and R^E is H; or R^E is



and R^D is H;

[0010] R^1 is —NHR^2 or —$NHCHR^2R^3$;

[0011] R^2 is —C_3-C_6alkyl or —C_4-C_6alkyl;

[0012] R^3 is L_1OH;

[0013] L_1 is —$(CH_2)_m$—;

[0014] L_2 is —$(CH_2)_n$—, —$((CH_2)_nO)_t(CH_2)_n$—, —$(CH_2)_nX_1(CH_2)_n$—, —$(CH_2)_nNHC(=O)(CH_2)_n$—, —$(CH_2)_nNHC(=O)(CH_2)_nC(=O)NH(CH_2)_n$—, —$((CH_2)_nO)_t(CH_2)_nNHC(=O)(CH_2)_n$, —$C(=O)(CH_2)_n$—, —$C(=O)((CH_2)_nO)_t(CH_2)_n$—, —$C(=O)((CH_2)_nO)_t(CH_2)_nX_1(CH_2)_n$—, —$C(=O)((CH_2)_nO)_t(CH_2)_nNHC(=O)(CH_2)_n$—, —$C(=O)((CH_2)_nO)_t(CH_2)_nC(=O)NH(CH_2)_n$—, —$C(=O)NH((CH_2)_nO)_t(CH_2)_nX_1(CH_2)_n$—, —$C(=O)X_2X_3C(=O)((CH_2)_nO)_t(CH_2)_n$—, —$C(=O)X_2X_3C(=O)(CH_2)_n$—, —$C(=O)X_2C(=O)(CH_2)_nNHC(=O)(CH_2)_n$—, —$C(=O)X_2C(=O)(CH_2)_nNHC(=O)((CH_2)_nO)_t(CH_2)_n$—, —$C(=O)(CH_2)_nC(R_7)_2$—, —$C(=O)(CH_2)_nC(R_7)_2SS(CH_2)_nNHC(=O)(CH_2)_n$—, —$(CH_2)_nX_2C$